REMARKS

The amendments to the specification add no new matter.

With entry of the current amendment, claims 48, 49, 52, and 55-58 have been amended and claims 50, 51, and 53 have been cancelled. Thus, claims 48, 49, 52, and 54-58 are pending in the application.

The amendments to the claims add no new matter and are fully supported throughout the application as filed.

Claim 48 has been amended to recite that an increase in the level of the polynucleotide relative to normal breast tissue is indicative of cancer. Support for this amendment can be found, *e.g.*, in Figure 36 and on page 17, lines 17-19.

Claim 49 has been amended to recite that the polynucleotide encodes the amino acid sequence of SEQ ID NO:25. Support for the amendment can be found, *e.g.*, in Figure 33 and 34.

Claim 52 has been amended to recite a step of isolating nucleic acids from the sample. Support for the amendment can be found, *e.g.*, on page 41, lines 8-25.

Claim 55 has been amended to recite that the detecting step comprises hybridizing a labeled probe to the polynucleotide. Support for the amendment can be found, *e.g.*, on page 42, lines 9-24.

Claim 57 has been amended to recite that the detecting step comprises hybridizing the polynutodie to a probe that is immobilized on a solid surface. Support for the amendment can be found, *e.g.*, on page 42, lines 9-24.

For convenience, the Examiner's objection/rejections are addressed in the order presented in the Office Action mailed December 4, 2002.

Priority

The application has been amended to provide the priority information in the first paragraph.

Applicants note that the claims currently under examination, which are drawn to SEQ ID NO:23, are supported in the priority application US Application No. 09/450,810, filed November 29, 1999. Support in the priority application can be found, *e.g.*, on the second to the last page of Figure 8, 5th entry from the bottom, which shows that a sequence corresponding to accession number W72838 is overexpressed in breast cancer compared to normal. This accession number is also set forth in Figure 10, first entry on page 14, of the instant application which further discloses that this accession number corresponds to BCH1 (*see* also, *e.g.*, Figure 12, first entry).

Objections to the specification

The amendment filed October 16, 2001 was objected to as allegedly introducing new matter into the disclosure of the invention. The objection alleges that the sequences set forth in SEQ ID NOs:54-62 of the new sequence listing were not disclosed in the application as filed. The Examiner argues that Figure 10 as filed provides Accession Nos., but not the actually sequences shown in the sequence listing. She is requiring that the sequences be cancelled or that declaratory evidence be presented that demonstrates that the sequences added to the specification constitute the particular sequences that corresponded to these accession numbers at the time the invention was made. Applicants respectfully request that this issue be held in abeyance until the identification of allowable claims, at which time Applicants will cancel the matter in question or provide the required declaratory evidence.

The specification was also objected to for embedded hyperlinks. The paragraphs noted by the Examiner have been amended to remove the hyperlinks. Applicants believe that there are no additional hyperlinks in the application.

The Examiner also noted the use of the trademark GeneChip™ in the application. The application has been amended to capitalize the trademark and include a generic terminology.

The Examiner alleges that the title of the invention is not descriptive of the elected invention. The invention has been re-titled as suggested by the Examiner.

Lastly, claims 48-58 were objected to for informalities involving punctuation. Claim 48 has been amended in accordance with the Examiner's suggestion.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 48-58 were rejected as allegedly not enabled. The Examiner alleges that the claims are not enabled for detecting cancer by any of the following: the detection of any polynucleotide encoding BCH1; the detection of "a level" of BCH1 polynucleotide; the detection of polynucleotides other than mRNA; or the detection of BCH1 in any tissue other than human breast tissue. To the extent that the rejection applies to the amended claims, Applicant's respectively traverse.

The Examiner contends that the claims are not enabled for the detection of any polynucleotide having at least 95% identity to SEQ ID NO:23 that encodes BCH1, because it is unpredictable whether such sequences are overexpressed in breast cancer relative to normal. The current invention involves detecting overexpression of the mRNA as recited in the claims in breast cancer in comparison to normal breast tissue for the detection of cancer. The specification teaches how to perform such an analysis (*see, e.g.,* page 42, lines 9-24). Moreover, Applicants present data showing that BCH1 mRNA sequences are overexpressed in individual breast tumor samples relative to normal (*see, e.g.,* Figures 36 and 38 and the "Examples" section). Applicants note that the current claims are drawn to nucleic acid sequences having at least 95% identity to the reference sequence. Such sequences are even more closely related on the polypeptide sequence level. Accordingly, this recitation covers sequences such as allelic variants. Applicants submit that based on the teachings in the specification, one of skill could reasonably predict that such closely related variants would also be diagnostic of breast cancer in individual patient samples. Applicants therefore respectfully request withdrawal of the rejection.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 48-58 were rejected as allegedly indefinite in the recitation of a number of terms. To the extent that the rejection applies to the amended claims, Applicants respectfully traverse. The rejections are individually addressed below.

"Diagnosing breast cancer in a patient"

Claims 48-58 were rejected as allegedly indefinite in the recitation of "diagnosing breast cancer in a patient". The Examiner argues that the claims do not clearly indicate how the detecting of step relates to or results in "diagnosing breast cancer is a patient." Although Applicants submit that the claim as filed is clear in view of the teachings in the specification, in order to expedite prosecution, claim 48 has been amended to recite that detection of overexpression of the polynucleotide is indicative of breast cancer. Applicants therefore respectfully request withdrawal of the rejection.

"Detecting the level of a polynucleotide encoding a BCH1 polypeptide"

The rejection alleges that the claims are unclear with regard to "the level" of the polypeptide and what must be detected in order to meet the requirements of the claim. In order to expedite prosecution, claim 48 has been amended to recite that an increase in the polynucleotide relative to normal breast tissue is indicative of cancer. Applicants therefore respectfully request withdrawal of the rejection.

"encoding a BCH1 polypeptide"

Claims 48-58 were rejected as allegedly indefinite over the recitation of the phrase "encoding a BCH1 polypeptide". The rejection alleges that "BCH1" does not provide any particular structural or functional property and it is unclear as to how this term is intended to further limit the claims. Applicants respectfully traverse. The specification provides a definition of a BCH1 polypeptide. The claim provides an additional element that further characterizes a polynucleotide (95% identity to SEQ ID NO:23) that encodes such a polypeptide. According to the MPEP § 2173.02, definiteness must be analyzed in light of: (A) the content of the application disclosure; (B) the teachings of the prior art, and (C) the claim interpretation that would be given by one of ordinary skill in the art. The rejection does not provide any evidence as to why one of skill would not consider the percent identity of the nucleic acid to a reference sequence to reflect a structural feature of a BCH1 polypeptide. Applicants therefore respectfully request withdrawal of the rejection.

"wherein the sample comprises isolated nucleic acids"

Claims 52 and 53 were rejected as allegedly indefinite over the recitationof the phrase "wherein the sample comprises isolated nucleic acids". Applicants note that the basis of the Examiner's contention that a biological sample from a patient must be unprocessed is not clear. However, in order to expedite prosecution, claim 53 has been amended to recite that the method further comprises a step of isolating nucleic acids from the sample. Applicants therefore respectfully request withdrawal of the rejection.

"wherein the nucleic acid is labeled"

Claims 55 and 56 were rejected as allegedly indefinite over the recitation of "wherein the polynucleotide is labeled". The Examiner points out that the polynucleotide is located in the biological sample. Although Applicants note that a polynucleotide from a sample, *e.g.*, an amplification product, can be labeled and hybridized to a probe, in order to expedite prosecution, claim 55 has been amended to recite that the detecting step comprises hybridizing a labeled probe to the polynucleotide. Applicants therefore respectfully request withdrawal of the rejection.

"the label"

Claim 56 was rejected as allegedly indefinite over the recitation of the limitation "the label." Although Applicants disagree, in order to expedite prosecution claims 55 and 56 have been amended, thereby obviating the rejection. Applicants therefore respectfully request its withdrawal.

"wherein the polynculetoide is immobilized on a solid surface"

Claim 57 was rejected as allegedly indefinite over the recitation of the limitation "wherein the polynucleotide is immobilized on a solid surface." In order to expedite prosecution, the claim has been amended to recite that the detecting step comprises hybridizing the

polynucleotide to a probe that is immobilized on the surface, thereby obviating the rejection. Applicants therefore respectfully request its withdrawal.

"the detection step"

Claim 58 was rejected as allegedly indefinite over the recitation of the term "the detection step." The rejection argues that there is insufficient antecedent basis for this limitation. Although Applicants disagree in that no reasoning is provided as to why a detection step provides insufficient antecedent basis for the detection of a nucleic acid, the claim has been amended, thereby obviating the rejection. Applicants therefore respectfully request its withdrawal.

Rejections under 35 U.S.C. § 103

Claims 48-53 and 55-57 were rejected as allegedly obvious over Reed *et al.* in view of Khan *et al.* The rejection alleges that Reed *et al.* disclose methods of detecting and diagnosing breast cancer in a patient in which a biological sample is obtained form the patient where the presence of a DNA molecule having the sequence of SEQ ID NO:56 is detected. This sequence is 95.2% identical to SEQ ID NO:23 of the instant application. The Examiner further characterizes Reed *et al.* as describing that SEQ ID NO:56 is over-expressed in breast tumor tissues and expressed at low levels in normal tissue. Although the Examiner acknowledges that Reed *et al.* do not teach the analysis of individual patient samples and the determination that the sequence at issue is overexpressed in individual breast tumors relative to normal, she alleges that the claimed invention is *prima facie* obvious. In particular, she argues that because Reed *et al.* disclose that SEQ ID NO:56 may be expressed at low levels in normal tissue, an ordinary artisan would have been motivated to have modified the method of Reed *et al.* so as to have determined the level of SEQ ID NO:56 mRNA and other breast-cancer associated mRNAs in a sample in order to differentiate between healthy cells expressing low levels of SEQ ID NO:56 and cancerous cells having increased expression of SEQ ID NO:56. Applicants respectfully traverse. The argument does not establish a proper case of *prima facie* obviousness because although one

skill might be tempted to perform the analysis suggested by the Examiner, there is no reasonable expectation of success based on the teachings in the cited art.

The sequence at issue in Reed *et al.* was identified in a subtraction library that is enriched for sequences expressed in breast tumor cells. Subtractive hybridization was performed using a library generated from cDNA prepared from a pool of RNA from three patients and a library from normal breast tissue from four patients. Clones from the subtracted library were analyzed (page 29-30). Reed *et al.* states that twenty one distinct cDNA clones were found to be over-expressed in breast tumor and expressed at low levels in all normal tissues tested. However, it is not clear how this analysis was performed. The only description of how the sequence at issue was "determined" to be over-expressed in breast tumors is that it is from the breast tumor subtraction library. There is no disclosure that the sequences were confirmed to be overexpressed in individual breast tumor samples. Indeed, there is no description or confirmation of overexpression of this sequence in any tissue or cell other than in the library. As the Examiner knows, "obvious to try" is not a proper basis for an obviousness rejection. In the absence of confirming studies, how could one of skill conclude that this sequence can be used diagnostically with any reasonable expectation of success?

The rejection further alleges that in view of the disclosure of Kahn *et al.*, which describes microarray methods for the simultaneous analysis of the expression of multiple genes to facilitate analysis of multiple samples, one of skill would have been motivated to use such a method to analyze multiple samples from a patient or patients. However, as explained above, the teachings of Reed *et al.* are defective in providing a basis for performing such an analysis. Kahn *et al.* do not cure this defect. Thus, the claims are not obvious over the combination of Reed *et al.* and Kahn et al.

Claims 48-53 were rejected as allegedly obvious over Reed *et al.* in view of Hackl *et al.* Hackl *et al.* describe RT-PCR analysis of breast tumor tissues samples and indicate that this method is more sensitive than detecting proteins. However, this references does not cure the defects noted above in Reed *et al.* Therefore, the claims are not obvious over the combination of the references.

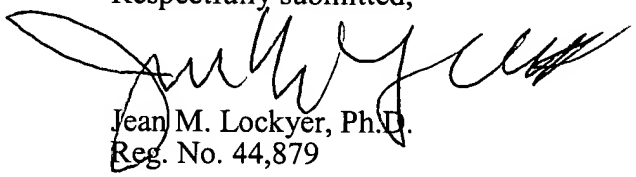
In view of the foregoing, the rejections applied to claims 48-53 and 55-57 do not establish a proper case of *prima facie* obviousness. Applicants therefore respectfully request withdrawal of the rejections.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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